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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Office Action Summary	Application No. 10/024,944	Applicant(s) BOLES ET AL.	
	Examiner Juliet Einsmann	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 19 December 2001 .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-5,8,10-12,19,20,24,26,29,30,40,42-44 and 50 is/are pending in the application.

4a) Of the above claim(s) 44 and 50 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-5,8,10-12,19,20,24,26,29,30,40,42 and 43 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Priority

1. This application is a continuation of 09/336609, now abandoned. A preliminary amendment was filed canceling claims 6, 7, 9, 13-18, 21-23, 25, 27, 28, 31-39, 41, and 45-49, and amending claim 19. It is noted that the preliminary amendment contained an additional amendment that was not entered because it is unclear what claim applicant intended to amend. The clean copy of the claim (on page 3 of the preliminary amendment) numbered the claim as 35. The marked up copy of the claim numbered the claim as 41. The text of the claim did not match the text of claim 35 or 41, and furthermore, both claim 35 and claim 41 were cancelled in the same preliminary amendment. Thus, the amendment was not enterable.

2. Claims 1-5, 8, 10-12, 19-20, 24, 26, 29-30, 40, 42-44, and 50 are pending in the application.

Election/Restrictions

3. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-5, 8, 10-12, 19-20, 24, 26, 29-30, 40, 42 and 43, drawn to methods for detection of a non-viral organism, classified in class 435, subclass 6.

II. Claims 44 and 50, drawn to kits for detecting a non-viral organism, classified in class 536, subclass 24.32.

The inventions are distinct, each from the other because of the following reasons:

4. Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the

product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the kits containing probes of group II could be used in different methods, including different detection methods or to synthesize polypeptides.

5. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as demonstrated by their different classification and recognized divergent subject matter and because inventions I-II require different searches that are not coextensive, examination of these claims would pose a serious burden on the examiner and therefore restriction for examination purposes as indicated is proper.

6. During a telephone conversation with Jennifer Camacho on 2/28/02 a provisional election was made with traverse to prosecute the invention of group 1, claims 1-5, 8, 10-12, 19-20, 24, 26, 29-30, 40, 42 and 43. Affirmation of this election must be made by applicant in replying to this Office action. Claims 44 and 50 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

7. Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

8. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the

application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification

9. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on at least page 14. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-5, 8, 10-12, 19-20, 24, 26, 29-30, 40, 42 and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-5, 8, 10-12, 19-20, 24, 26, 29-30, 40, 42 and 43 are indefinite for failing to recite a final process step which agrees back with the preamble. Claims 1-5, 8, 10-12, 19-20, 24, 26, 29-30, 40, 42 and 43 are drawn to a method for detecting a non-viral organism in a sample, yet the claims recite a final step of detecting hybridization of a probe. The claims do not set forth the relationship between the detecting hybridization of a probe and the detecting a non-viral organism in a sample and therefore, it is not clear whether the claims are intended to be drawn to a method for detecting a non-viral organism in a sample or a method for detecting hybridization

of a probe. Amendment of the claims to read e.g. "wherein the hybridization of the probe is indicative of the presence of said non-viral organism" would obviate this rejection.

Claims 1-5, 8, 10-12, 19-20, 24, 26, 29-30, 40, 42 and 43 are indefinite over the recitation of "substantially complementary" because the claims do not provide a clear definition of this term or a method for determining such a level of complementarity. While the specification, at page 9, defines the term "substantially complementary" this definition is not sufficient to clearly provide limitations for this term. Particularly, the specification notes that this term refers to a nucleic acid sequent which will hybridize to the complement of another nucleic acid strand under "stringent conditions" and further the specification notes that one of skill in the art would know how to adjust stringent conditions to allow for higher or lower percent mismatch between two nucleic acids. The phrase "stringent conditions" is a non-limiting phrase because all hybridization conditions are stringent conditions, although they may vary as to the level of stringency. Since the specification lacks a clear definition of the term "substantially complementary" the metes and bounds of these claims cannot be determined.

Claims 4, 5, 20, 24, 26, 29, 30, 42, and 43 are indefinite over the recitation of "stringent conditions" because it is not clear what limitation applicant is intending to impart with the use of this language because all hybridization conditions are stringent conditions, although they may vary as to the level of stringency.

Claims 26, 29, 30, 42, and 43 are indefinite over the recitation "the nucleic acid probe" because claim 20 recites two different nucleic acid probes, on in step (i) and one in step (ii). It is not clear to which probe these claims are referring.

Claim 24 is indefinite because it is unclear which "step of contacting" is meant as base claim 20 has two separate contacting steps.

Claim 40 is indefinite because it depends from a cancelled claim. Therefore, it is unclear what the claim encompasses.

Claim 43 recites the limitation "the adaptor" in line 1. There is insufficient antecedent basis for this limitation in the claim. While claim 26 recites an adaptor probe, claim 26 does not specifically recite or define "the adaptor."

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claim 40 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

14. This rejection applies to claim 40 insofar as it would require SRP RNA from organisms belonging to specifically listed genuses of protozoa, fungi and bacteria. The practice of this invention requires knowledge of the specific sequences of the SRP RNA of these organisms in order to design probes for use in their detection. The specification does not provide specific

disclosure of the sequences of SRP RNA for these genuses, and further, these sequences would not have been known to one of ordinary skill in the art at the time the invention was made because Zwieb et al. (Nucleic Acids Research, 2000, Vol. 28, No. 1 (171-172)) teach all known SRP RNA sequences and these species are not included in their database. Furthermore and extensive search of commercial databases revealed that these sequences are not disclosed in the prior art. As such, the specification lacks sufficient written description of the claimed invention. The examiner is aware that the SRP RNA sequences for some of the claimed genuses are available in the prior art (*Bacillus, Pseudomonas, Chlamydia, Chlostridia, Escherichia, Helicobacter, Legionella, Haemophilus, Trypanosoma,* and *Ureaplasma*), and these are considered to have met the written description requirement. This rejection applies to claim 40 with regard to those groups claimed for which there has been no disclosure of the appropriate nucleic acid sequences either in the instant specification or in the prior art.

15. Claim 19 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods which utilize nucleic acid probes comprising SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 11, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 22, SEQ ID NO: 24, and SEQ ID NO: 25, does not reasonably provide enablement for methods which utilize nucleic acid probes comprising SEQ ID NO: 21, SEQ ID NO: 23, and SEQ ID NO: 26 . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to methods for detecting in a sample a non-viral organism, said methods utilizing a nucleic acid probe that is substantially complementary to a subsequence of SRP RNA from the group of non-viral organisms. The rejected claim recites a number of probes in particular, and this rejection is written to specifically address probes which comprise SEQ ID NO: 21, SEQ ID NO: 23, and SEQ ID NO: 26. The claims are drawn using open claim language to describe the probes, because the claim recites that "the nucleic acid probe has…," and the transitional phrase "has" is understood to have identical meaning to the phrase "comprising."

The prior art teaches the nucleic acid sequence for the SRP RNA of a number of different organisms (see, for example, Zwieb et al. (Nucleic Acids Research, 2000, Vol. 28, No. 1 (171-172)). In particular, the prior art provides the nucleic acid sequence of a number of Bacillus species (Nakamura *et al.*) and the SRP RNA sequence from E. coli (Griffin *et al.* and Larsen *et al.*). With regard to SEQ ID NO: 21, SEQ ID NO: 23, and SEQ ID NO: 26, however, the examiner was unable to identify any prior art that teaches a SRP RNA sequence that comprises these particular sequences. Sequence searches demonstrated, however, that these fragments are found within a variety of different nucleic acids from some viral and some non-viral organisms. For example, SEQ ID NO: 21 is found with the mitochondrial DNA of hummigbirds and warblers (hits numbered 2 and 5 on result list), it is found within an mRNA from a goldfish retina (hit number 5), and it is found within the Sendai virus genome (hit number 15)(see attached result table from a sequence search of SEQ ID NO: 21). Furthermore, 100% hit matches to SEQ ID NO: 21 are found within the human genome (hits 32-45). The fragments

represented by SEQ ID NO: 23 and SEQ ID NO: 25 are also found in a variety of different organisms, including human sequences, but do not appear to be found in the SRP RNA of any organism whose SRP RNA sequence was known at the time the invention was made.

The instant specification does not discuss SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 25. The recitation of these sequences first appears in claim 19. Thus, the specification provides no specific guidance as to which organism's SRP RNA these sequence target, and therefore what organisms one could expect to detect by the use of these probes. The specification thus provides no guidance to the ordinary practitioner as to how to use these particular probes in a nucleic acid assay for the detection of a non-viral organisms using a probe that is specific to SRP RNA.

The level of unpredictability with regard to identifying an appropriate target for these sequences is quite high. One would have to be able to make an assessment based solely on the order of the nucleotides in the sequence. Considering that there are hundreds of thousands of non-viral organisms, and that these particular sequences do not appear to match up to the SRP RNA of any known non-viral organisms, essentially one would have to guess what organism these sequences are designed to target. Furthermore, if one were using a sample from a human, for example, it would be likely that a probe comprising one of these sequences would hybridize to a portion of the human genome. And for SEQ ID NO: 21, it is possible that this sequence will not only hybridize to non-viral organisms nucleic acids, but also to the genome of some viral organisms.

The quantity of experimentation required to determine how to use an the instantly claimed invention with nucleic acid probes comprising SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 26 is quite high. Considering all of the different types of non-viral organisms, the ordinary practitioner would have to undertake the identification, isolation, and sequencing of the SRP RNA from an unknown number of organisms until at least one organism whose SRP RNA matches these sequences is identified. After such an identification, the ordinary practitioner would be required to then be required to confirm the specificity of the probe by the additional screening of samples to determine the scope of the group of organisms for which the probe is specific.

The specification does not provide any working examples which utilize probes having SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 26.

Considering all of these factors, it is concluded that undue experimentation would be required to practice the claimed invention utilizing probes comprising SEQ ID NO: 21, SEQ ID NO: 23, and SEQ ID NO: 26, in particular.

Claim Rejections - 35 USC § 103

16. Claims 1-2, 4-5, 8, 10, 12, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. (US 5595874) in view of Nakamura et al. (Nucleic Acids Research 20(19): 5227-5228).

Hogan et al. teach methods for the identification of non-viral organisms in samples, including human blood samples (Col. 1, line 30) using hybridization probes to RNA. This

method comprises the steps of (i) contacting a sample with more than one labeled nucleic acid probe (Col. 28, lines 1-8, 18-21) (ii) incubating the sample comprising the sample and the RNA under conditions to allow a hybrid to form (Col. 28, lines 25-27) and (iii) detecting the hybridization products (Col. 28, lines 35-40). The probes taught by Hogan et al. include DNA probes (Col. 8, line 20). Hogan *et al.* further provide methods in which more than one probe to the target sequence is utilized (Example 8). Furthermore, Hogan et al. provide specific instructions for the selection of probes:

> "Once the variable regions are identified, the sequences are aligned to reveal areas of maximum homology or 'match'. At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics.
>
> First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate Tm. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a Tm about 2-10°C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided (Col. 6, line 50-Col. 7, line11)."

Hogan et al. do not teach the use of this method using SRP RNA to detect a group of non-viral organisms.

Nakamura et al. teach sequence of the SRP RNA (the scRNA) for ten species of *Bacillus*, and further provide an alignment of these sequences (see Fig. 1). Nakamura et al. point out that there is a block containing complete primary sequence identity which corresponds to nucleotides 154-175 of the *B. subtilis* scRNA (p. 5227). Instantly disclosed SEQ ID NO: 2 consists of the complement of nucleotides 154-175 of the *B. subtilis* sequence, and instantly disclosed SEQ ID NO: 3, 4 , and 5 are smaller portions of this region. Instant SEQ ID NO: 25 is identical to nucleotides 151-163 of the B. thurigiensis scRNA taught by Nakamura *et al.* and instant SEQ ID NO: 24 is identical to nucleotides 151-163 of the B. brevis sequence (numbering according to the B. subtilis sequence).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have probes comprising the SRP RNA taught by Nakamura et al. in the detection method taught by Hogan et al. In light of the teachings of Nakamura et al. which specifically point to a region of the SRP RNA that is conserved among Bacillus species and demonstrates via the alignment regions of the genome that are particular to different Bacillus species, and the clear teachings on probe selection and the use of nucleic acid probes provided by Hogan et al., the ordinary practitioner would have been motivated to select probes from the 21 base pair conserved region of the *Bacillus* genome in order to have created a rapid and effective method for detecting *Bacillus*. Additionally, the ordinary practitioner would have been motivated to select probes from outside of this conserved region to develop species specific probes, since Hogan *et al.* also provide guidance as to how to make species specific probes. One would be motivated to detect *Bacillus* in a sample, and particularly a human sample since some

species of *Bacillus* are pathogenic to humans, for example *B. cerus*. The combination of the teachings of Hogan et al. with those of Nakamura et al. would have resulted in a rapid and effective method for detecting *Bacillus* in a sample, and thus the claimed invention is *prima facie* obvious in view of the teachings of Hogan *et al.* and Nakamura *et al.*

17. Claims 1-2, 4-5, 8, 10-12, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. (US 5595874) in view Griffin (Journal of Biological Chemistry (1975) 250(14):5426-5437).

Hogan et al. teach methods for the identification of non-viral organisms in samples, including human blood samples (Col. 1, line 30) using hybridization probes to RNA. This method comprises the steps of (i) contacting a sample with more than one labeled nucleic acid probe (Col. 28, lines 1-8, 18-21) (ii) incubating the sample comprising the sample and the RNA under conditions to allow a hybrid to form (Col. 28, lines 25-27) and (iii) detecting the hybridization products (Col. 28, lines 35-40). The probes taught by Hogan et al. include DNA probes (Col. 8, line 20). Hogan *et al.* further provide methods in which more than one probe to the target sequence is utilized (Example 8). Furthermore, Hogan et al. provide specific instructions for the selection of probes:

> "Once the variable regions are identified, the sequences are aligned to reveal areas of maximum homology or 'match'. At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics..
>
> First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions

> of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate Tm. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a Tm about 2-10°C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided (Col. 6, line 50-Col. 7, line11)."

Hogan et al. do not teach the use of this method using SRP RNA to detect a group of non-viral organisms.

Griffin teaches sequence of 4.5 S RNA from *E. coli* (Abstract, Fig. 10) and that the 4.5 S RNA has been shown to be a component of a number of strains of E. coli. Instant SEQ ID NO: 6 consists of the complement of nucleotides 37-59 of this sequence, instant SEQ ID NO: 22 consists of the complement of nucleotides 40-52, and instant SEQ ID NO: 9 of the complement of nucleotides 65-82. Therefore, the 110 base pair RNA disclosed by Griffin comprises instant SEQ ID NO: 6, 22, and 9.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have selected probes from the 4.5 S RNA taught by Griffin for the detection of E. coli in the methods taught by Hogan et al. in order to have created a method for the detection of E. coli. The ordinary practitioner would have been motivated to have used the SRP RNA because Griffin teaches that this RNA has been shown to be a component of a number of strains of E. coli, and Hogan *et al.* teach methods for the detection of non-viral organisms which utilize probes to conserved RNA sequences in the target organism. Furthermore, the

ordinary practitioner would have been motivated to detect E. coli in a sample, including a human sample, because some E. coli are pathogenic to humans.

18. Claims 1-2, 4-5, 8, 10-12, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. (US 5595874) in view of Larsen et al. (Nucleic Acids Research 19(2) 209-215).

Hogan et al. teach methods for the identification of non-viral organisms in samples, including human blood samples (Col. 1, line 30) using hybridization probes to RNA. This method comprises the steps of (i) contacting a sample with more than one labeled nucleic acid probe (Col. 28, lines 1-8, 18-21) (ii) incubating the sample comprising the sample and the RNA under conditions to allow a hybrid to form (Col. 28, lines 25-27) and (iii) detecting the hybridization products (Col. 28, lines 35-40). The probes taught by Hogan et al. include DNA probes (Col. 8, line 20). Hogan *et al.* further provide methods in which more than one probe to the target sequence is utilized (Example 8). Furthermore, Hogan et al. provide specific instructions for the selection of probes:

> "Once the variable regions are identified, the sequences are aligned to reveal areas of maximum homology or 'match'. At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics.
>
> First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by

terminating the hybrids with G:C base pairs and by designing the probe with an appropriate Tm. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a Tm about 2-10°C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided (Col. 6, line 50-Col. 7, line11)."

Hogan et al. do not teach the use of this method using SRP RNA to detect a group of non-viral organisms.

Larsen et al. teach the sequences of SRP RNA from 39 species of organisms, including the 4.5S RNA of E. coli. Instant SEQ ID NO: 6 consists of the complement of nucleotides 37-59 of this sequence, instant SEQ ID NO: 22 consists of the complement of nucleotides 40-52, and instant SEQ ID NO: 9 consists of the complement of SEQ ID NO: 65-82. Therefore, the E. coli RNA disclosed by Larsen et al. comprises instant SEQ ID NO: 6, 22, and 9. Larsen et al. also teach the SRP RNA sequence from a fungus, specifically, the yeast *Schizosaccaromyces pombe*.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the alignment provided by Larsen et al. and the clear instructions on probe selection provided by Hogan et al. in order to have selected probes useful in the methods taught by Hogan et al. for the detection of any one of the species disclosed by Larsen et al. It would have been further obvious to have used such probes to detect, for example, E. coli in humans since E. coli is a pathogen to humans. An ordinary practitioner would have been motivated to develop such a detection assay in order to have provided a rapid method for screening for pathogens in samples.

19. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over any one of the following:

(A) Hogan et al. in view of Nakamura et al. as applied to claims 1-2, 4-8, 10, 12, 17-19, 52, 53, 56, 57, and 58 above, and further in view of Rudert et al.

(B) Hogan et al. in view of Griffin et al. as applied to claims 1-2, 4-8, 10-12, 17-19, 52, 53, 56, 57, and 58 above, and further in view of Rudert et al.

(C) Hogan et al. in view of Larsen et al. as applied to claims 1-2, 4-8, 10-13, 17-19, 52, 53, 56, 57, and 58 above, and further in view of Rudert et al.

The teachings of all of the above combinations are applied to this rejection as discussed in the previous rejections. These teachings do not teach methods in which the SRP RNA is labeled.

Rudert et al. teach that the reverse dot blot technique is useful for detecting nucleic acid sequences, and that in this technique sample nucleic acids are labeled and hybridized to probes bound to a solid support (Col. 3, lines 1-5).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used a reverse dot-blot technique in the methods taught by reference combinations A-C and thus have labeled the SRP RNA. An ordinary practitioner would have been motivated to use such a technique because Rudert et al. specifically teach that the reverse dot blot technique has advantages which include the ability to screen with many specific probes at the same time simultaneously and in the same container, only one preparation is required to

label a large amount of sample nucleic acid and thus, simple and direct comparison of the results between different probes is possible (Col. 3, lines 10-26).

20. Claims 20, 24, 29-30, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. in view of Nakamura et al. as applied to claims 1-2, 4-5, 8, 10, 12, and 19 above, and further in view of Ghosh *et al.* (US 5237016).

The teachings of Hogan et al. in view of Nakamura et al. are applied to this rejection as discussed in the previous rejections. Hogan et al. in view of Nakamura et al. do not teach contacting the duplex SRP RNA with a gel-immobilized nucleic acid probe and detecting the hybridization product.

Ghosh *et al.* teach sandwich hybridization assays which comprise the steps of

(i) contacting a sample comprising target RNA with a nucleic acid probe, wherein the nucleic acid probe is substantially complementary to a subsequence of the target RNA and wherein the nucleic acid probe has the ability to hybridize to the target RNA (Col. 12, lines 25-30);

(ii) incubating the sample comprising the target RNA and the nucleic acid probe under stringent hybridization conditions to form a duplex (Col. 12, lines 25-30);

(iii) contacting the duplex with a gel-immobilized nucleic acid probe (Col. 12, lines 31-36);

(iv) incubating the duplex and the gel-immobilized nucleic acid probe under hybridization conditions such that the gel-immobilized nucleic acid probe (Col. 12, lines 31-36); and

(v) detecting hybridization of the gel-immobilized probe to the target duplex (Table XI, Col. 25, for example).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the sandwich hybridization assay taught by Ghosh *et al.* in combination with the methods provided by Nakamura *et al.* in view of Hogan *et al.* The ordinary practitioner would have been motivated to combine these methods because Ghosh *et al.* teach that target nucleic acid may detected by oligonucleotides immobilized on solid supports using "sandwich" hybridization systems, using capture oligonucleotides for capturing detection oligonucleotide-target nucleic acid adducts formed in solution (Col. 1, lines 50-53). Ghosh *et al.* further teach that their methodology utilizing gel immobilized probes reduces non-specific bacground in contrast to dextran beads (Col. 25, table XI, and lines 58-68).

21. Claims 20, 24, 30, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. in view of Griffin et al. as applied to claims 1-2, 4-5, 8, 10-12, and 19 above, and further in view of Ghosh *et al.* (US 5237016).

The teachings of Hogan et al. in view of Griffin et al. are applied to this rejection as they are applied above. Hogan et al. in view of Griffin et al. do not teach contacting the duplex SRP RNA with a gel-immobilized nucleic acid probe and detecting the hybridization product.

Ghosh *et al.* teach sandwich hybridization assays which comprise the steps of

(i) contacting a sample comprising target RNA with a nucleic acid probe, wherein the nucleic acid probe is substantially complementary to a subsequence of the target RNA and

wherein the nucleic acid probe has the ability to hybridize to the target RNA (Col. 12, lines 25-30);

(ii) incubating the sample comprising the target RNA and the nucleic acid probe under stringent hybridization conditions to form a duplex (Col. 12, lines 25-30);

(iii) contacting the duplex with a gel-immobilized nucleic acid probe (Col. 12, lines 31-36);

(iv) incubating the duplex and the gel-immobilized nucleic acid probe under hybridization conditions such that the gel-immobilized nucleic acid probe (Col. 12, lines 31-36); and

(v) detecting hybridization of the gel-immobilized probe to the target duplex (Table XI, Col. 25, for example).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the sandwich hybridization assay taught by Ghosh *et al.* in combination with the methods provided by Griffin *et al.* in view of Hogan *et al.* The ordinary practitioner would have been motivated to combine these methods because Ghosh *et al.* teach that target nucleic acid may detected by oligonucleotides immobilized on solid supports using "sandwich" hybridization systems, using capture oligonucleotides for capturing detection oligonucleotide-target nucleic acid adducts formed in solution (Col. 1, lines 50-53). Ghosh *et al.* further teach that their methodology utilizing gel immobilized probes reduces non-specific bacground in contrast to dextran beads (Col. 25, table XI, and lines 58-68).

22. Claims 20, 24, 29-30, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. in view of Larsen et al. as applied to claims 1-2, 4-5, 8, 10-12, and 19 above, and further in view of Ghosh *et al.* (US 5237016).

The teachings of Hogan et al. in view of Larsen et al. are applied to this rejection as discussed in the previous rejections. Hogan et al. in view of Larsen et al. do not teach contacting the duplex SRP RNA with a gel-immobilized nucleic acid probe and detecting the hybridization product.

Ghosh *et al.* teach sandwich hybridization assays which comprise the steps of

(i) contacting a sample comprising target RNA with a nucleic acid probe, wherein the nucleic acid probe is substantially complementary to a subsequence of the target RNA and wherein the nucleic acid probe has the ability to hybridize to the target RNA (Col. 12, lines 25-30);

(ii) incubating the sample comprising the target RNA and the nucleic acid probe under stringent hybridization conditions to form a duplex (Col. 12, lines 25-30);

(iii) contacting the duplex with a gel-immobilized nucleic acid probe (Col. 12, lines 31-36);

(iv) incubating the duplex and the gel-immobilized nucleic acid probe under hybridization conditions such that the gel-immobilized nucleic acid probe (Col. 12, lines 31-36); and

(v) detecting hybridization of the gel-immobilized probe to the target duplex (Table XI, Col. 25, for example).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the sandwich hybridization assay taught by Ghosh *et al.* in combination with the methods provided by Larsen *et al.* in view of Hogan *et al.* The ordinary practitioner would have been motivated to combine these methods because Ghosh *et al.* teach that target nucleic acid may detected by oligonucleotides immobilized on solid supports using "sandwich" hybridization systems, using capture oligonucleotides for capturing detection oligonucleotide-target nucleic acid adducts formed in solution (Col. 1, lines 50-53). Ghosh *et al.* further teach that their methodology utilizing gel immobilized probes reduces non-specific bacground in contrast to dextran beads (Col. 25, table XI, and lines 58-68).

23. Claims 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over any one of the following:

(A) Hogan et al. in view of Nakamura *et al.*, and further in view of Ghosh *et al.* as applied to claims 20, 24, 29-30, and 40 above, and further in view of Urdea et al.

(B) Hogan et al. in view of Griffin et al., and further in view of Ghosh *et al.* as applied to claims 20, 24, 30, and 40 above, and further in view of Urdea et al.

(C) Hogan et al. in view of Larsen et al., and further in view of Ghosh *et al.* as applied to claims 20, 24, 29-30, and 40 above, and further in view of Urdea et al.

The teachings of all of the above combinations are applied to this rejection as outlined above. These teachings do not teach methods in which the nucleic acid probe is an adaptor probe comprising a subsequence of that hybridizes to the gel-immobilized probe.

Urdea et al. teach nucleic acid sandwich assays which utilize an adaptor probe which has regions that hybridize to both the sample and the immobilized probe (Col. 1, lines 50-53).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the probe taught by Urdea et al. in any one of the methods taught by A-C in order to have provided a more efficient capture based detection method since Urdea et al. teach that such a method is advantageous because "using combinations of nucleic acid sequences complementary to a nucleic acid analyte and to arbitrary sequences and specific binding pair members, a detectable label may be separated in two phases in proportion to he amount of analyte present in the sample (Col. 2, lines 29-24)."

Allowable Subject Matter

24. Claims 42 and 43 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claims 42 and 43 are free of the prior art because SEQ ID NO: 7 and 8, one of which is required for the claims, are free of the prior art. These sequences are "adaptor probes" comprising a sequence specific for the target SRP RNA and an arbitrary sequence specific for a capture probe. While Urdea *et al.* describes such adaptor probes, Urdea *et al.* does not provide the specific sequence of the adaptor portion of SEQ ID NO: 7 and 8. These adaptor sequences are not provided in the prior art.

Conclusion

25. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The complemetn of instant SEQ ID NO: 11 consists of the complement of nucleotides is contained in the disclosure of E. coli 4.5 S RNA by Hsu *et al.* (J. Mol. Biol. (1984) 178(3) 509-31). Rejections utilizing these reference would have been duplicative of those rejections already of record.

26. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

27. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Einsmann whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Juliet C. Einsmann
Examiner
Art Unit 1655

March 11, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600

This is a result summary from a sequence search of SEQ ID NO: 21 against an EMBL/GENBANK database. The ID numbers in the table are GenBank accession numbers. The "Description column" provides a short description of the nucleic acid disclosed in the GenBank record. In the 112 1st paragraph rejection, the "hit" numbers are referring to the "Result No." column in the table.

SUMMARIES

	Result No.	Score	% Query Match	Length	DB	ID	Description	Pred. No.
	1	12	100.0	166	32	MMAPLB3	Mus musculus apolipopr	6.00e+02
	2	12	100.0	250	24	LNCYTOB2	Lesbia nuna cytochrome	6.00e+02
	3	12	100.0	515	21	TPGAPC2	T.pyriformis mRNA for	6.00e+02
	4	12	100.0	1041	24	PFMY10729	P.fuscatus mitochondri	6.00e+02
c	5	12	100.0	1102	24	CRAVIA1	Carassius auratus vime	6.00e+02
c	6	12	100.0	1104	21	DROANNIX	D.melanogaster annexin	6.00e+02
	7	12	100.0	1143	24	MIEFCYTB	E.fastuosus mitochondr	6.00e+02
	8	12	100.0	1785	25	I06678	Sequence 1 from Patent	6.00e+02
c	9	12	100.0	2157	32	RNU63971	Rattus norvegicus rhod	6.00e+02
c	10	12	100.0	3210	21	DMREPO	D.melanogaster mRNA fo	6.00e+02
c	11	12	100.0	3225	25	I82816	Sequence 13 from paten	6.00e+02
c	12	12	100.0	3320	25	A66551	Sequence 1 from Patent	6.00e+02
	13	12	100.0	3710	21	DROUMPS	Drosophila melanogaste	6.00e+02
c	14	12	100.0	3883	17	BMU10241	Brucella melitensis 16	6.00e+02
c	15	12	100.0	5824	37	PAMYXSEN	Sendai virus genome RN	6.00e+02
c	16	12	100.0	7808	37	PERY17013	Porcine endogenous ret	6.00e+02
c	17	12	100.0	8196	25	A66552	Sequence 2 from Patent	6.00e+02
c	18	12	100.0	8209	25	A66553	Sequence 3 from Patent	6.00e+02
	19	12	100.0	11904	17	AE001008	Archaeoglobus fulgidus	6.00e+02
c	20	12	100.0	16026	17	D90769	E.coli genomic DNA, Ko	6.00e+02
	21	12	100.0	24323	21	CELK06A5	Caenorhabditis elegans	6.00e+02
	22	12	100.0	34820	26	AF085222	Streptococcus thermoph	6.00e+02
c	23	12	100.0	34869	22	CELH32C10	Caenorhabditis elegans	6.00e+02
	24	12	100.0	37768	21	CELF53B3	Caenorhabditis elegans	6.00e+02
c	25	12	100.0	43986	31	AC004206	Homo sapiens clone UWG	6.00e+02
	26	12	100.0	47739	18	AF017113	Bacillus subtilis 300-	6.00e+02
c	27	12	100.0	49804	22	AC006303	Drosophila melanogaste	6.00e+02
	28	12	100.0	53339	18	EAU67194	Enterobacter aerogenes	6.00e+02
c	29	12	100.0	65025	19	AC005712	Drosophila melanogaste	6.00e+02
	30	12	100.0	97451	28	F19K23	Sequence of BAC F19K23	6.00e+02
	31	12	100.0	99688	28	ATF13M23	Arabidopsis thaliana D	6.00e+02
c	32	12	100.0	119351	19	HS74M1	Human DNA sequence ***	6.00e+02
c	33	12	100.0	122823	31	AC005996	Homo sapiens PAC clone	6.00e+02
c	34	12	100.0	127282	31	AC005155	Homo sapiens PAC clone	6.00e+02
	35	12	100.0	128460	19	HS782L23	Human DNA sequence ***	6.00e+02
	36	12	100.0	136222	20	AC006477	Homo sapiens clone DJ0	6.00e+02
	37	12	100.0	138317	20	AC006404	WORKING DRAFT SEQUENCE	6.00e+02

c	38	12	100.0	147552	20	AC006966	Homo sapiens clone DJ0	6.00e+02
	39	12	100.0	148627	19	AC006447	WORKING DRAFT SEQUENCE	6.00e+02
c	40	12	100.0	156089	19	AC004586	Human Chromosome 15q26	6.00e+02
c	41	12	100.0	160358	20	AC006495	Drosophila melanogaste	6.00e+02
	42	12	100.0	163595	19	HS745I14	Human DNA sequence ***	6.00e+02
c	43	12	100.0	183521	20	AC007044	Homo sapiens clone RG4	6.00e+02
	44	12	100.0	197491	20	AC007000	Homo sapiens clone NH0	6.00e+02
	45	12	100.0	241859	19	HS996D20	Human DNA sequence ***	6.00e+02

This is a result summary from a sequence search of SEQ ID NO: 23 against an EMBL/GENBANK database. Only 100% hits are provided. The ID numbers in the table are GenBank accession numbers. The "Description column" provides a short description of the nucleic acid disclosed in the GenBank record. In the 112 1st paragraph rejection, the "hit" numbers are referring to the "Result No." column in the table.

SUMMARIES

	Result No.	Score	% Query Match	Length	DB	ID	Description	Pred. No.
c	1	13	100.0	749	31	HOMOSLC9	Homo sapiens neuronal	1.13e+02
	2	13	100.0	2677	31	AF005654	Homo sapiens actin-bin	1.13e+02
c	3	13	100.0	3813	17	BACRPL1	Bacillus subtilis gene	1.13e+02
c	4	13	100.0	4620	18	BSU43929	Bacillus subtilis ribo	1.13e+02
	5	13	100.0	4760	32	AF024524	Mus musculus LIM domai	1.13e+02
	6	13	100.0	6754	29	HUMORFKG1L	Human mRNA for KIAA005	1.13e+02
c	7	13	100.0	35445	17	MLCB2052	Mycobacterium leprae c	1.13e+02
	8	13	100.0	115863	19	HS268D13	Human DNA sequence ***	1.13e+02
	9	13	100.0	118595	29	HS288L1	Human DNA sequence fro	1.13e+02
	10	13	100.0	128270	19	HS444C7	Human DNA sequence ***	1.13e+02
	11	13	100.0	135395	20	AC006325	Homo sapiens clone GS2	1.13e+02
	12	13	100.0	144820	19	AC005280	Homo sapiens clone DJ0	1.13e+02
c	13	13	100.0	144857	19	AP000036	Homo sapiens genomic D	1.13e+02
	14	13	100.0	146831	29	HS523C21	Homo sapiens DNA seque	1.13e+02
	15	13	100.0	147708	29	HS179M20	Human DNA sequence fro	1.13e+02
	16	13	100.0	147752	19	HS836J3	Human DNA sequence ***	1.13e+02
c	17	13	100.0	159500	32	AC005742	Mus musculus chromosom	1.13e+02
c	18	13	100.0	169325	31	AC007065	Homo sapiens, clone hR	1.13e+02
	19	13	100.0	170891	19	AC002118	Genomic sequence from	1.13e+02
	20	13	100.0	176186	31	AC006925	Homo sapiens chromosom	1.13e+02
	21	13	100.0	177137	19	AC005089	Homo sapiens clone RG3	1.13e+02
c	22	13	100.0	183507	20	AC007093	Homo sapiens clone NH0	1.13e+02
c	23	13	100.0	213080	17	BSUB0001	Bacillus subtilis comp	1.13e+02
	24	13	100.0	287723	20	AC006449	Homo sapiens chromosom	1.13e+02
	25	13	100.0	306131	19	AC006874	Caenorhabditis elegans	1.13e+02

This is a result summary from a sequence search of SEQ ID NO: 26 against an EMBL/GENBANK database. Only 100% hits are provided. The ID numbers in the table are GenBank accession numbers. The "Description column" provides a short description of the nucleic acid disclosed in the GenBank record. In the 112 1st paragraph rejection, the "hit" numbers are referring to the "Result No." column in the table.

	Result No.	Score	Query Match	Length	DB	ID	Description	Pred. No.
c	1	13	100.0	7872	17	BAAMYLA	B.acidocaldarius amy g	5.36e+01
	2	13	100.0	122199	19	HS1000N6	Human DNA sequence ***	5.36e+01
	3	13	100.0	155176	29	HS453P22	Human DNA sequence fro	5.36e+01